IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: JORDAN, Heather	Confirmation No. 1446
Application No.: 09/613,903	Examiner: SISSON, Bradley
Filed: July 11, 2000	Docket No: IVGN 187.1 CON
For: NUCLEIC ACID LADDERS	Technology Center/Art Unit: 1634
Customer No.: 52059	**APPELLANT'S BRIEF UNDER 37 CFR §41.37**

Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

This brief is filed pursuant to 37 C.F.R. §41.37, following the Notice of Appeal received by the USPTO on October 10, 2011. Also submitted with this brief is a petition to extend time to response for two months (from December 10, 2011, to February 10, 2012) and authorization to pay the fee as set forth in 37 C.F.R. §41.20(b)(2).

TABLE OF CONTENTS

I. REAL PARTY IN INTEREST 3

II. RELATED APPEALS AND INTERFERENCES 3

III. STATUS OF CLAIMS 3

IV. STATUS OF AMENDMENTS 3

V. SUMMARY OF CLAIMED SUBJECT MATTER 3

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL 5

VII. ARGUMENTS 5

VIII. CONCLUSION 11

IX. CLAIMS APPENDIX 12

X. EVIDENCE APPENDIX 16

XI. RELATED PROCEEDINGS APPENDIX 17

I. REAL PARTY IN INTEREST

The real party in interest in U.S. Application No. 09/613,903 is Life Technologies Corporation, the assignee of the entire right of the present application.

II. RELATED APPEALS AND INTERFERENCES

There are no other pending appeals by Appellants or interferences in which Appellants are involved, the outcome of which would directly affect the decision by the Board of Patent Appeals and Interferences in this pending appeal.

III. STATUS OF CLAIMS

Claims 1-42 were originally filed. Claims 1-42 were subsequently canceled and claims replaced by claims 43-64. Claims 43-64 were canceled and replaced by claims 65-139. Claims 65-84 were subsequently canceled and claim 140 was added. Claims 85-140 were canceled and claims 141-173 were added. Claims 142-149, 151-154, 160 and 161 were canceled. Claims 141, 150, 155-159 and 162-173 were pending and were rejected. Claims 141, 150, 155-159 and 162-173 are presently under appeal.

IV. STATUS OF AMENDMENTS

No claim amendments were made subsequent to the Final Office Action mailed May 10, 2011.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter in this appeal relates to compositions comprising a plurality of double stranded nucleic acid compositions, or ladders, which may be used as standards for estimating the size (in base pairs) and or mass of nucleic acid molecules of unknown size and/or mass.

As defined by independent claims, which are summarized below, the compositions are characterized in that the relative mass any one of the nucleic acid molecules comprising the composition is no more than three times the relative mass of any of the other nucleic acid molecules comprising the composition. The result of this feature is that, when resolved by electrophoresis and visualized using a nucleic acid stain, the relative intensity of each "band" corresponding to nucleic acid molecules of a specific size is no more than three times the intensity of any other "band".

Claim 141

The subject matter claimed in independent claim 141 is a nucleic acid ladder consisting essentially of a plurality of double stranded nucleic acid fragments (page 4, lines 21-25; page 7, last

paragraph; and page 8, 4th paragraph), each fragment having a size in base pairs of between 20 kb and 100 base pairs (page 4, line 30 – page 5, line 12), a copy number, a mass, and a relative mass wherein the mass of each fragment is the size in base pairs of the fragment multiplied by the copy number of the fragment (page 8, last paragraph), wherein the relative mass of each fragment is the mass of the fragment divided by the sum of the masses of all of the fragments (page 9, second paragraph), wherein the relative mass of any one fragment of the plurality is no more than 3 time the relative mass of any other fragment of the plurality (page 9, lines 8-15; and Figure 2), wherein at least two of the plurality of nucleic acid fragments have a size greater than 1 kb, and wherein at least two of the plurality of nucleic acid fragments have a size less than 1 kb (page 9, last sentence – page 10, first paragraph; page 13, last paragraph – page 14, line 4; and Figure 2).

Claim 165

The subject matter claimed in independent claim 165 is a nucleic acid ladder comprising a plurality of double stranded nucleic acid molecules, wherein three or more of the molecules are of a size selected from the group consisting of: (a) 100 base pairs, (b) 200 base pairs, (c) 300 base pairs, (d) 400 base pairs, (e) 500 base pairs, (f) 650 base pairs, (g) 850 base pairs, and (h) 1650 base pairs (Figure 2; Example 2; Table 1; page 5, last paragraph);

wherein two or more of the molecules are of a size selected from the group consisting of: (a) 1 kilobase pairs, (b) 2 kilobase pairs, (c) 3 kilobase pairs, (d) 4 kilobase pairs, and (e) 5 kilobase pairs (Figure 2; Example 2; Table 1; page 5, last paragraph);

wherein a copy number of each of the molecules is such that each molecule has a relative mass that is no more than three times the relative mass of another molecule (page 9, lines 8-15; and Figure 2).

Claim 169

The subject matter claimed in independent claim 169 is a nucleic acid ladder comprising a plurality of double stranded nucleic acid molecules, wherein three or more of the molecules are of a size selected from the group consisting of: (a) 100 base pairs, (b) 200 base pairs, (c) 300 base pairs, (d) 400 base pairs, (e) 500 base pairs, (f) 650 base pairs, (g) 850 base pairs, and (h) 1650 base pairs; (Figure 2; Example 2; Table 1; page 5, last paragraph); wherein two or more of the molecules are of a size selected from the group consisting of: (a) 1 kilobase pairs, (b) 2 kilobase pairs, (c) 3 kilobase pairs, (d) 4 kilobase pairs, and (e) 5 kilobase pairs (Figure 2; Example 2; Table 1; page 5, last paragraph); wherein a copy number of the molecules is such that each molecule has a relative mass that is no more than three times the relative mass of another molecule and one or both of the following (page 9, lines 8-15; and Figure 2);

i) wherein the nucleic acid ladder further comprises at least one highlight fragment having a size in the range of 100 base pairs to 5 kilobase pairs and having a relative mass that is three times greater than the relative mass of other molecules in the composition, or (page 14, first full paragraph; Figure 2); ii) wherein at least one of the three or more molecules is a highlight fragment having a relative mass that is three times greater than the relative mass of the other molecules in the composition (page 14, first full paragraph).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

There remains one ground of rejection. Namely, the rejection of claims 141, 150, 155-157, 159 and 162-173 under 35 U.S.C. §103(a) for alleged obviousness over either US Patent No. 5,316,908 ("Carlson"), or Stratagene 1993 or Stratagene Catalog (1993) is maintained from the previous Office Action.

VII. ARGUMENTS

A. The Obviousness Rejection over Carlson Is Improper

Claims 141, 150, 155-157, 159 and 162-173 stand rejected under 35 U.S.C. §103(a) for alleged obviousness over the Carlson reference. Appellants respectfully contend that the rejection is in error and request its reversal.

To establish a *prima facie* case of obviousness, three basic criteria must be met: first, the prior art references must teach or suggest all the claim limitations; second, there must be some suggestion or motivation, either in the references or in the knowledge generally available to one of ordinary skill in the art, to combine the limitations; third, there must be a reasonable expectation of success in combining the limitations. MPEP §2143. The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d 1385, 1395-97 (2007) identified several rationales to support a conclusion of obviousness. The key to supporting any rejection under 35 U.S.C. §103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. §103 should be made explicit. Appellant contends that neither the Carlson reference nor the two Stratagene references satisfy this standard.

The claimed invention defined by independent claim 141, which the Examiner regards as representative and against which the majority of arguments against patentability have been made, is a nucleic acid ladder consisting essentially of a plurality of double stranded nucleic acid fragments, each fragment having a size in base pairs of between 20 kb and 100 base pairs, a copy number, a mass, and a relative mass wherein the mass of each fragment is the size in base pairs of the fragment multiplied by the

copy number of the fragment, wherein the relative mass of each fragment is the mass of the fragment divided by the sum of the masses of all of the fragments, wherein the relative mass of any one fragment of the plurality is no more than 3 time the relative mass of any other fragment of the plurality, wherein at least two of the plurality of nucleic acid fragments have a size greater than 1 kb, and wherein at least two of the plurality of nucleic acid fragments have a size less than 1 kb.

In contrast, the Carlson reference is entitled "Size Markers for Electrophoretic Analysis of DNA" and generally describes "a DNA marker ladder useful in Southern blot hybridizations … made up of **pooled DNA restriction endonuclease digests**, where each restriction digest contains at least one fragment complementary to a probe and at least one fragment not complementary to the probe. The regions of complementarity between the probe and the complementary fragments are double-stranded segments of the fragments. The ladder is characterized by an approximately even spacing of bands, resulting from choosing fragments having an logarithmic size distribution. Kits incorporating this ladder and a probe or means for making a probe or a probe and a means for labeling a probe are also disclosed" (Carlson, Abstract; *Emphasis added*).

1. Carlson Fails to Teach Or Suggest All The Claims Limitation

Claim 141 recites a combination of features that include "a copy number, a mass, and a relative mass wherein the mass of each fragment is the size in base pairs of the fragment multiplied by the copy number of the fragment, wherein the relative mass of each fragment is the mass of the fragment divided by the sum of the masses of all of the fragments, wherein the relative mass of any one fragment of the plurality is no more than 3 time the relative mass of any other fragment of the plurality", in combination with the remaining features set forth in the claim.

Appellant contends that Carlson fails to teach or suggest such a combination of features. In fact, Carlson *et al.* fails to disclose any relationship amongst the individual nucleic acid fragments. As noted at column 2, lines 21-23 of Carlson *et al.*, "FIG. 1 is a schematic scale drawing of how the first and second molecular marker kits would migrate on an electrophoretic gel." One skilled in the art would recognize that a ***schematic*** drawing of the migration pattern of DNA bands on an electrophoretic gel would not convey any information whatsoever beyond how different sized bands migrate along the length of the gel. Appellants assert that Carlson's schematic diagram fails to convey any information relating to staining intensity, copy number or total mass of the nucleic acid present in any individual band or bands. Further, Carlson specifically teaches altering the copy number of the largest and the smallest fragments in the ladder by increasing their copy number relative to the copy number of the middle range fragments (column 5, lines 55-63 of Carlson *et al.*). This alteration is described by Carlson *et al.* as one that overcomes the poor hybridization efficiency of the larger fragments and the poor retention of the smaller

fragments on a membrane. If one were to increase the copy number of the larger fragments relative to the medium sized fragments (as described by Carlson *et al.*), both the relative mass and the total mass of the larger fragments would be increased in comparison to other fragments in the ladder. Because the claims require that "the relative mass of any one fragment of the plurality is no more than 3 time the relative mass of any other fragment of the plurality", Carlson *et al.* fails to disclose all of the limitations of these claims.

In addition, as discussed above, the increase in copy number of the larger fragments compared to the medium-sized fragments would lead to an increase in the relative mass or the total mass of the larger fragments, rather than a mass that is substantially equal as claimed herein. Appellants have demonstrated in Figure 2 of the instant application that several commercially available nucleic acid ladders meet this size requirement. However, neither this figure or the other ladders disclosed in Figure 2, describe the relative mass requirements recited in the instant claims. Figure 1 of Carlson merely lists a range of nucleic acid fragments, irrespective of the relative mass of each of those fragments. Furthermore, as evidenced by the multitude of commercially-available DNA ladders disclosed in Figure 2 of the specification that fail to meet this requirement, the need had not been met in the art. Thus, the Examiner has failed to provide a *prima facie* case of obviousness.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 102(b) or 35 U.S.C. § 103(a).

2. No Motivation to Modify Carlson As Suggested

The Examiner contends that the highly schematized representation of what Carlson's nucleic acid looks like when electrophoretically resolved and stained that is depicted in Figure 1 of Carlson (reproduced below for convenience) "disclose(s) a nucleic acid ladder that comprises multiple nucleic acid fragments that have the same intensity" (Final Office action, page 4, section 12). The Examiner further states "[w]hile Fig. 1 is a drawing and not a photograph, the specification does state that the Figure does represent the migration of the nucleic acid ladder in an electrophoretic environment. Said Figure clearly shows that the band have the same relative intensity" (Office action, page 5, section 14).

A. Carlson's Figure 1 Is A Schematic Drawing And Does Not Reflect The True Appearance Of The Ladder After Electrophoretic Resolution

Appellant respectfully disagrees with these rejections and submits that the interpretation of Carlson's Fig. 1 is incorrect for at least the following reasons. First, Fig. 1 of Carlson is not photographic

representation of the DNA markers that are disclosed. Instead, Fig. 1 is a "schematic, scale drawing of how the first and second molecular markers ***would migrate*** on an electrophoresis gel" (Carlson, Col. 2, lines 21-23; *Emphasis added*). There is no indication in Carlson that the diagram shown in Figure 1 is attempting to convey any information other the relative migration pattern of each individual band. In fact, as discussed in greater detail below, a reading of the remainder of Carlson's disclosure, specifically relating to how the subject DNA ladder was made (i.e., by "pooling" a plurality of individual restriction digests while keeping the copy number, i.e., "dose" at 1 (see Carlson, TABLE 3)) directly contradicts the Examiner's erroneous contention that the bands depicted in Carlson are of substantially equal intensity. A schematic drawing, by its very definition, represents elements of a system (e.g., band of a molecular weight ladder) using abstract, graphic symbols rather than realistic pictures.

A schematic usually omits all details that are not relevant to the information the schematic is intended to convey, and may even add unrealistic elements that aid comprehension. Carlson's Fig. 1 is a drawing and the information represented in the drawing is prophetic. The drawing is meant to convey information relating to electrophoretic *migration* of the individual bands through a gel. There is nothing in Fig. 1 or in any of Carlson's disclosure that relates to or conveys any information about the *mass* of DNA in individual bands, as defined in the instant claims. The Examiner makes this very admission on page 5 of the Office action, noting "Fig. 1 is a drawing and not a photograph, the specification does state that the Figure does represent the *migration* of the nucleic acid ladder in an electrophoretic environment. Said Figure clearly shows that the bands have the same relative intensity" (Office action, page 5, section 14; Emphasis added). Therefore, by the Examiner's *own admission*, Carlson's Fig. 1 is merely a schematic representation of the migration of DNA bands, and is not an accurate representation of what the ladders actually look like during an electrophoresis experiment. Appellant submits that it is improper to extrapolate information relating to the **mass** of individual bands (which relates to the band's intensity) using Fig.1, since the intent thereof was to represent band migration (i.e., band size), not mass (i.e., DNA content).

Moreover, the very nature by which Carlson's DNA markers are made (i.e., by restriction digestion of a single larger λ-page DNA) is not conducive to the Examiner's interpretation of Fig. 1. In this regard Carlson clearly states "[t]he ladder is made up of pooled DNA restriction endonuclease digests" (Abstract). Carlson further states "[t]o make a restriction digest, λ DNA was digested with one or two restriction endonucleases. The enzymes used for individual digests are indicated in Tables 2 and 3. Digestions were performed under standard conditions, generally according to the instructions of the enzyme's manufacturer. Restriction digests were pooled after digestion" (Carlson, Col. 4, lines 58 – 64).

Therefore, if each band depicted in Fig. 1 were of equal intensity, as the Examiner contends, then the ***copy number of each of the bands would have to have been adjusted to compensate***

for the decrease in DNA mass of each band, since the bands in a single digest are present in an equimolar ratio (i.e., assuming complete digestion of the λ-page DNA, mole equivalent of each of the resulting bands is 1:1…:1).

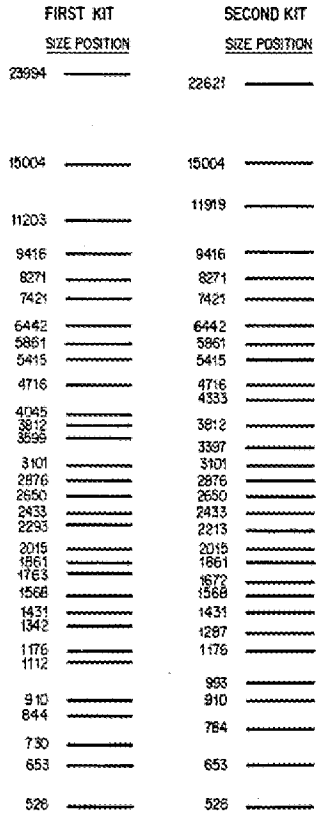
There is no indication or suggestion in Carlson that the copy number of the bands were adjusted so that the bands would show up on an electrophoresis gel with equal intensity. In fact, in Example 2 (First Marker Kit), Carlson explicitly states "[i]n the first ladder, the target DNA consisted of pooled *equal* amounts of 31 different restriction digests of phage λ DNA" (Carlson, Col. 4, last sentence; Emphasis added). If the input λ DNA of each digest was equal, as Carlson states, then each band should be visualized with its appropriate mass intensity, which was ***not adjusted***. Yet, the intensity of each band constituting the molecular weight marker on the left side of Fig. 1 is shown as equal, reinforcing Appellant's assertion that Fig. 1 is not a realistic representation of Carlson's marker set. In fact, the only indication that Carlson adjusted the amount of any of the individual bands in the marker set is found in Example 3: Second Marker Kit, which states in part "[t]he third improvement was to increase the amounts, i.e. relative copy number or the dosage, of the target DNA for the largest and smallest bands. Large DNA fragments blot inefficiently. As is well known in the art, small fragments are retained on membranes poorly during hybridization. Therefore, the signal from large DNA fragments and small DNA fragments tends to be less than the signal from bands in the middle range. This improvement compensated for that effect" (Carlson, Col. 5, lines 55-60).

Additionally, Table 3 (Carlson, Col. 7) outlines the size of each DNA fragment appearing on the right hand side of Fig. 1, along with its dosage compensation (either 3 for the largest and smalles fragmants, or 1 for all the fragments ranging in size between 5.8 kb abd 910 bp). According to Table 3, the smallest 526 bp fragment and the largest 22.6 kb fragment are present in **equimolar** amounts (i.e., 3-fold), which means that the 22.6 kb band contains 43-fold as much DNA on mass basis as the 526 bp band, yet both bands are represented with equal intensity in Fig. 1. The only way that the bands could have shown up with equal intensity, is if Carlson adusted the copy number of the DNA bands so that the amount of DNA in each band on a mass basis was approximately equal. Carlson makes no indication that this was done, a fact that is repeatedly ignored by the Examiner's sole focus on Figure 1.

Additionally, if the 6.4 kb Ava II band is compared with the 5.8 kb Hae II band, both of which are similar to each other in size and which are depicted in Fig. 1 as bands with equal intensity, we see that the 6.4 kB Ava II band actually has 3.3-fold the amount (i.e., mass) of DNA present in the 5.8 kb Hae II band (i.e., compare the 3 fold dose of the 6.4 kb band with the 1-fold dose of the 5.8 kb band). Despite this large differential in the actual amount of DNA present in each band, Carlson depicts the bands as having equal intensity in Fig. 1. Similarly, the 910 bp Eco RV/Bam HI band is compared with the 784 bp Dde I band, both of which are similar in size and which are depicted in Fig. 1 as bands with

equal intensity, we see that the smaller 784 bp Dde I band actually has 2.6-fold the amount (i.e., mass) of DNA as the larger 910 bp Eco RV/Bam HI band (i.e., compare the 3 fold dose of the Dde I band with the 1-fold dose of the Eco RV/Bam HI band). The above serves to illustrate the fact that there is no correlation between the size, mass or relative mass and the depicted band intensity of the fragments shown in Carlson's Fig. 1, and no conclusion about same can be made.

(Carlson, Figure 1)



B. The Examiner Has Ignored Teachings in Carlson That Conflict With His Interpretation of Figure 1

On page 11, section 31 of the Office Action, the Examiner states "[i]t is noted that the applicant has not indicated how anything about the illustration is technically flawed or that the conclusions drawn therefrom cannot be sustained by the teachings of the prior art".

Appellant contends that this statement is completely erroneous. The arguments presented above relating to the technical flaws with the Examiner's arguments have been presented to the Examiner repeatedly, seemingly to no avail since the Examiner has never addressed or properly rebutted same. The very same arguments presented above were submitted to the Examiner in the response to final office action submitted on May 24, 2010. Yet in the subsequent Office action, none of Appellant's rebuttal

arguments presented above were addressed. Instead, they were all summarily dismissed as "attorney argument", and Examiner's sole focus on Figure 1 resumed despite a substantial portion of Carlson's disclosure except for Figure 1 directly teaching away from this interpretation.

For at least the forgoing reasons, Appellants respectfully request the reversal of the obviousness rejections over the Carlson reference.

B. The Stratagene References Suffer From The Same Deficiencies As The Carlson Reference

The two Stratagene references are cited against the claims presumably for substantially the same reasons as the Carlson reference. Appellant rebuts the application of these references against the claims for substantially the same reasons outlined above and incorporated herein. In particular, Appellant notes that the Lambda/Hind III, pUC19/Taq I-pUC19/Sau 3A DNA Markers described in each of the references are also a product of restrictions digestion. There is no indication in references that the copy number of any of the fragment, or the relative mass of any of the fragments, was adjusted so that the ladder would fall within the scope of the present claims.

VIII. CONCLUSION

In view of the above discussions, Appellants respectfully submit that the obviousness rejections of the pending claims are erroneous and should therefore be reversed.

Respectfully submitted,

/Jonathan P. Aumais/
Jonathan P. Aumais, Ph.D.
Reg. No. 65,710
AGENT FOR APPLICANT(S)

LIFE TECHNOLOGIES CORPORATION
Intellectual Property Department
5981 Van Allen Way
Carlsbad, CA 92008
Phone: (760) 476-6271

Date: February 10, 2012

IX. CLAIMS APPENDIX

141. A nucleic acid ladder consisting essentially of a plurality of double stranded nucleic acid fragments, each fragment having a size in base pairs of between 20 kb and 100 base pairs, a copy number, a mass, and a relative mass wherein the mass of each fragment is the size in base pairs of the fragment multiplied by the copy number of the fragment, wherein the relative mass of each fragment is the mass of the fragment divided by the sum of the masses of all of the fragments, wherein the relative mass of any one fragment of the plurality is no more than 3 time the relative mass of any other fragment of the plurality, wherein at least two of the plurality of nucleic acid fragments have a size greater than 1 kb, and wherein at least two of the plurality of nucleic acid fragments have a size less than 1 kb.

150. The nucleic acid ladder of claim 141, wherein at least 3 of the plurality of double stranded nucleic acid fragments have a size greater than 1 kb, and wherein at least 3 of the double stranded nucleic acid fragments have a size less than 1 kb.

155. The nucleic acid ladder of claim 141, wherein at least 4 of the plurality of double stranded nucleic acid fragments have a size greater than 1 kb, and wherein at least 4 of the plurality of double stranded nucleic acid fragments have a size less than 1 kb.

156. The nucleic acid ladder of claim 141, wherein at least 5 of the plurality of double stranded nucleic acid fragments have a size greater than 1 kb, and wherein at least 5 of the plurality of double stranded nucleic acid fragments have a size less than 1 kb.

157. The nucleic acid ladder of claim 141, wherein the plurality of double stranded nucleic acid fragments are stained with a detectable label.

158. The nucleic acid ladder of claim 157, wherein the detectable label is [2-[N-(3-dimethylaminopropyl)-N-propylamino]-4-[2,3-dihydro-3-methyl-(benzo-1,3-thiazol-2-yl)-methylidene]-1-phenyl-quinolinium]+.

159. The nucleic acid ladder of claim 157, wherein the detectable label is ethidium bromide.

162. The nucleic acid ladder of claim 141, wherein the relative mass of any one fragment of the plurality is no more than 2.5 times the relative mass of any other fragment of the plurality.

163. The nucleic acid ladder of claim 141, wherein the relative mass of any one fragment of the plurality is no more than 2 times the relative mass of any other fragment of the plurality.

164. The nucleic acid ladder of claim 141, wherein the relative mass of any one fragment of the plurality is no more than 1.5 times the relative mass of any other fragment of the plurality.

165. A nucleic acid ladder comprising a plurality of double stranded nucleic acid molecules, wherein three or more of the molecules are of a size selected from the group consisting of:
(a) 100 base pairs,
(b) 200 base pairs,
(c) 300 base pairs,
(d) 400 base pairs,
(e) 500 base pairs,
(f) 650 base pairs,
(g) 850 base pairs, and
(h) 1650 base pairs;
wherein two or more of the molecules are of a size selected from the group consisting of:
(a) 1 kilobase pairs,
(b) 2 kilobase pairs,
(c) 3 kilobase pairs,
(d) 4 kilobase pairs, and
(e) 5 kilobase pairs;
wherein a copy number of each of the molecules is such that each molecule has a relative mass that is no more than three times the relative mass of another molecule.

166. The nucleic acid ladder of claim 165, wherein four or more of the fragments are between 100 base pairs and 1650 base pairs.

167. The nucleic acid ladder of claim 166, wherein five or more of the fragments are between 100 base pairs and 1650 base pairs.

168. The nucleic acid ladder of claim 166, wherein three or more of the fragments are between 1 kilobase pairs and 5 kilobase pairs.

169. A nucleic acid ladder comprising a plurality of double stranded nucleic acid molecules, wherein three or more of the molecules are of a size selected from the group consisting of:

(a) 100 base pairs,

(b) 200 base pairs,

(c) 300 base pairs,

(d) 400 base pairs,

(e) 500 base pairs,

(f) 650 base pairs,

(g) 850 base pairs, and

(h) 1650 base pairs;

wherein two or more of the molecules are of a size selected from the group consisting of:

(a) 1 kilobase pairs,

(b) 2 kilobase pairs,

(c) 3 kilobase pairs,

(d) 4 kilobase pairs, and

(e) 5 kilobase pairs;

wherein a copy number of the molecules is such that each molecule has a relative mass that is no more than three times the relative mass of another molecule and one or both of the following;

i) wherein the nucleic acid ladder further comprises at least one highlight fragment having a size in the range of 100 base pairs to 5 kilobase pairs and having a relative mass that is three times greater than the relative mass of other molecules in the composition, or;

ii) wherein at least one of the three or more molecules is a highlight fragment having a relative mass that is three times greater than the relative mass of the other molecules in the composition.

170. The nucleic acid ladder of claim 169, wherein four or more of the fragments are between 100 base pairs and 1650 base pairs.

171. The nucleic acid ladder of claim 169, wherein five or more of the fragments are between 100 base pairs and 1650 base pairs.

172. The nucleic acid ladder of claim 169, wherein three or more of the fragments are between 1 kilobase pairs and 5 kilobase pairs.

173. The nucleic acid ladder of claim 169, wherein the highlight fragment has a relative mass that is at least 5 times greater than the other fragments.

X. EVIDENCE APPENDIX

None.

XI. RELATED PROCEEDINGS APPENDIX

None.